Remarks

The Applicants note with appreciation the Examiner's interview on October 4, 2004 between Applicants' representative and Examiner. The Applicants further note with appreciation the Examiner's indication that Claim 11, drawn to an isolated and purified TWIK-1 protein consisting essentially of SEQ ID NO: 2, was allowable. Accordingly, the Applicants have amended Claim 11 to indicate the TWIK-1 consists essentially of SEQ ID NO: 2.

The Applicants have also cancelled Claim 28. Accordingly, Claims 11 and 27 are pending.

Objection to Specification

The Applicants have amended the Specification to consistently refer to the transmembrane domains as "M1-M4." Accordingly, page 7 of the Specification has been amended to change "T1-T4" to "M1-M4."

Double Patenting

The Applicants note with appreciation, the Examiner's abeyance of the rejection of Claims 11 and 27, and 28 as provisionally rejected under US Applications 09/436.265; 09/939,483; 09/939,484; and 09/892,360. The Applicants will address this provisional rejection upon issuance of the Claims from these pending applications, should that occur before allowance of the pending claims.

Claim Rejections under 35 U.S.C. § 101

The Applicants note with appreciation, the Examiner's withdrawal of the rejection of Claims 11, 27, and 28 for lacking utility under 35 U.S.C. § 101 as indicated in the Interview summary from the interview of October 4, 2004. In particular, the Applicants note that Claims 11, 27, and 28, which are drawn to SEQ ID NO: 2, and functionally equivalent derivatives

thereof, can be used for a number of purposes including drug screening. For example, one skilled in the art can use TWIK-1 or functionally equivalent derivatives thereof to screen for therapeutic compounds which inhibit or enhance TWIK-1 activity in tissue culture. In yet other examples, TWIK-1 or functionally equivalent derivatives thereof are useful in molecular diagnostics; for example, to screen for TWIK-1 defects in people suffering from arrhythmia disorders, or suffering from heart and or neuronal disorders involving potassium transport. Finally, TWIK-1 or functionally equivalent derivatives thereof can be used in therapeutic methods to treat individuals suffering from these disorders.

Claim Rejections under 35 U.S.C. § 112, first paragraph—enablement

Claim 27 and 28 have been rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to enable functionally equivalent derivatives of the TWIK-1 protein of SEQ ID NO: 2. Claim 28 has been cancelled and, as a result the rejection of Claim 28 is now moot. The Applicants submit that Claim 27 is enabled by the Specification

In particular, the Specification provides sufficient guidance and direction for one skilled in the art to select the Applicants' claimed functionally equivalent derivatives of SEQ ID NO: 2. The Applicants respectfully submit that Claim 27 recites functionally equivalent derivatives of SEQ ID NO: 2, which has well-defined structural characteristics that are unique to the claimed TWIK-1 proteins. Claim 27 also specifies that the claimed functionally equivalent derivatives of SEQ ID NO: 2 transports potassium across a membrane with weak inward rectification properties.

Thus, the claimed functionally equivalent derivatives of TWIK-1 must contain the following structural features recited in Claim 27:

- Two pore domains, P1 and P2

- Four transmembrane segments, M1, M2, M3, and M4
- An amino acid loop between the M1 and P1 domains containing potential N-glycosylation
- A phosphorylation consensus site at the N-terminus
- A phosphorylation consensus site at the C-terminus, and
- A phosphorylation consensus site between the M2 and M3 domains.

As demonstrated in Fig. 1B, the P1 and P2 domains and the M1, M2, M3, and M4 domains constitute nearly 50% (154 of 336 aa residues) of TWIK-1.

The sequence of SEQ ID No: 2, as shown in Figs. 1B and 2B, are the base sequence from which the claimed functionally equivalent TWIK-1 derivatives can be obtained by varying non-critical amino acid residues. The reliance on SEQ ID No: 2 as a base sequence, and the detailed structural and functional information recited in claim 27, allows one skilled in the art to readily identify candidate functionally equivalent derivatives of TWIK-1. These candidate proteins can then be assayed for functional activity as weak inward rectifiers of potassium, according to the protocol set forth on pages 9-13 of the Applicants' Specification.

The test for enablement requires an inquiry as to whether one skilled in the art can make or use the invention without undue experimentation. See MPEP 2164.01. It is well settled in the law that experimentation is **not** undue when the experimentation is routine. Hence, it is not undue for the skilled artisan to isolate candidate proteins that meet the structural requirements recited in Claim 27, and assay the candidate protein according to the procedures set forth in pages 9-13 of the Specification to determine if the candidate protein functions as inward rectifier of potassium (and thus falls within the scope of the claim).

For example, one skilled in the art could follow the protocol set forth in the Applicants' Specification on pages 13-14 and insert the coding sequence of the Applicants claimed functionally equivalent derivative of SEQ ID NO: 2 between the non-coding sequences 5' and 3'

of *Xenopus* globin in the vector pEXO. (See page 9 of the Specification). The skilled artisan could then take the complementary RNA (cDNA) that was transcribed from the vector construction and insert the RNA into the oocytes of *X.laevis*. Next, a non-inactivating current, free from non-injected cells, can be measured as a baseline. (See page 9 of the Specification). A candidate protein having the required structural characteristics of SEQ ID No: 2, but with non-critical variations, can then be subjected to the same tests, in order to determine whether it is indeed a functionally equivalent derivative of TWIK-1. Then, any of a number of functional activation/inactivation tests can be run, including those described on pages 9-13 of the Specification. Consequently, the Applicants submit that the Specification teaches one skilled in the art how to make and use the Applicants' claimed invention without undue experimentation. In view of the foregoing, the Applicants respectfully request withdrawal of the rejection of Claim 27 for lack of enablement.

Claim Rejections under 35 U.S.C. § 112, first paragraph—written description

Claims 27 and 28 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an adequate written description. Claim 28 has been cancelled and, as a result the rejection is now moot as to this claim.

The Applicants respectfully submit that one skilled in the art would readily understand that the Applicants were in possession of the claimed functionally equivalent derivatives recited in Claim 27.

The Applicants invite the Examiner's attention to the *Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement* ("the guidelines"), which state on page 1106 that:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, **structures**, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety ways including description of... relevant, **identifying characteristics**, structure or other physical and/or chemical properties, **by functional characteristics coupled with a known or disclosed correlation between function and structure**, or by a combination such identifying characteristics, sufficient to show the applicant was in possession of the claimed invention. [Emphasis added].

Here, the Applicants' claims functionally equivalent derivatives of SEQ ID NO: 2, which have weak inward rectification properties and a number of distinct identifying structural characteristics as recited in Claim 27:

- Two pore domains, P1 and P2
- Four transmembrane segments, M1, M2, M3, and M4
- An amino acid loop between the M1 and P1 domains containing potential N-glycosylation
- A phosphorylation consensus site at the N-terminus
- A phosphorylation consensus site at the C-terminus, and
- A phosphorylation consensus site between the M2 and M3 domains.

As discussed above, these structural characteristics are based on the sequence of SEQ ID No: 2, as shown in Fig. 1B. The claimed functionally equivalent derivatives have non-critical variations in the amino acid sequence of SEQ ID No: 2, which preserve the structural and functional characteristics of the protein, as recited in claim 27.

The claimed structural characteristics are known or disclosed to be correlated to the weak inward rectification of potassium. For example, the claimed functionally equivalent derivatives contain two P domains, which are well known to be an essential element of potassium-permeable channels (See page 2 of the Specification). Thus, for example, one of the structures of the Applicants claimed functionally equivalent derivatives - the two P domains - function to make the claimed functionally equivalent derivatives of TWIK-1 a potassium-permeable pore. Likewise, the four transmembrane segments allow the claimed functionally equivalent

derivatives of TWIK-1 to function as a potassium rectification channel. Consequently, one skilled in the art would readily understand that the Applicants were in possession of functionally equivalent TWIK-1 derivatives having distinct structural features (as derived from the SEQ ID No: 2 base sequence) that are correlated to a known or disclosed function. In view of the foregoing, the Applicants request withdrawal of the rejection of Claim 27 as allegedly failing to meet the written description requirement of 35 U.S.C. §112 first paragraph.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Applicants note with appreciation, the Examiner's intention to withdraw the rejection of Claims 11, 27, and 28 as indefinite under 35 U.S.C § 112, second paragraph, in light of the points raised by the Applicants' representative in the interview of October 4, 2004. In particular the Applicants claim a protein, TWIK-1, which is referred to in the claim preamble by the English language convention as "***T***andem of P domains in a ***W***eak ***I***nward rectifying ***K***+ channel." [Emphasis added]. (See page 3 of the Applicants' Specification).

Thus, the Applicants named their new channel protein according to well-accepted English naming convention standards that are well recognized in the art, as indicated in the Applicant's Specification at page 3. Accordingly, the Applicants submit that the terminology in Claims 11 and 27 is well understood by those skilled in the art. Withdrawal of the rejection of Claims 11 and 27 as indefinite under 35 U.S.C § 112, second paragraph, is therefore respectfully requested.

The Applicants submit that the Application is now in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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